US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 559

THE RELATIONSHIP BETWEEN THE ANALGETIC EFFECT OF MORPHINE AND ADDICTION LIABILITY IN RATS

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UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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The animals used in this study were handled in accordance with the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

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Internal Medicine
USAMRL Project No. 6X60-01-001

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ABSTRACT

THE RELATIONSHIP BETWEEN THE ANALGETIC EFFECT OF MORPHINE AND ADDICTION LIABILITY IN RATS

OBJECT

The purpose of this study was to determine the effect of morphine as an analgetic agent on addiction-prone and addiction-resistant rats. Naive animals, from strains with demonstrated differences in addiction liability, were tested using the "jump-flinch" procedure to determine if any differences existed in their sensitivity to the analgetic effect of morphine.

RESULTS AND CONCLUSION

It was found that the dose-response curves for addiction-prone and addiction-resistant animals differed both in terms of the slope of the curves and in mean threshold values. The addiction-prone animals profited most from the administration of the opiate. This demonstration of a relationship between addiction liability and response to the analgetic effect of morphine suggests an approach for further research to determine if addiction liability can be predicted upon the basis of sensitivity to the analgetic effect of opiate drugs.

RECOMMENDATIONS

It is recommended that animals from other strains be tested to determine their sensitivities to the analgetic effect of morphine. Upon completion of this testing, the most sensitive and the least sensitive animals would then be tested for addiction liability. This procedure would allow a determination of the use of analgetic testing as a predictive tool in the study of addiction.

APPROVED: 

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I. INTRODUCTION

Drug addiction, as a disease of behavior, is beginning to yield to the application of behavioral methods. From this point of view, a procedure has been devised by which rats can be caused to develop sustained opiate-directed behavior (1). Consequent to this procedure, it has been shown that individual animals vary in the degree to which they are subject to an addicting effect of opiates. Using the drinking tube procedure developed by Nichols (2), the individual variability in the opiate-seeking response has been brought under study. By selective inbreeding of animals which have a strong tendency to sustain an opiate-directed behavior and those animals which evidenced a relatively weak tendency, it has been demonstrated that strains of rats can be developed with differential degrees of opiate-seeking behavior. It has also been demonstrated that these strain differences are not due to weight, to an impairment in the taste sense or in the emotionality of the strains which were developed by this procedure. Thus, at this point, the research stands as having developed strains of rats with differing degrees of opiate-directed behavior. However, as yet, no other characteristics, either behavioral or physiological, have been related to the addiction-prone or addiction-resistance of these strains.

The purpose of the present study was to determine the relationship between the addiction liability and the degree to which these animals would profit from an injection of morphine in a painful situation. Thus, the question was asked, does a relationship exist between the effect of morphine as an analgetic agent and morphine as an addicting drug.

II. METHOD

Sixteen naive male albino rats from the colony of Southeastern Louisiana College, ranging in age from approximately 124 to 127 days, were studied. Their weights varied between 300 and 400 grams. Of these animals, eight were from the strain which had been demonstrated to be addiction-prone and eight were of the strain which had been shown to be addiction-resistant. The animals were coded in such a manner that the investigator who tested the analgesic response was uninformed as to which animals belonged to which strain.

The method used to test the analgetic effect of morphine on these animals was a modification of the "jump-flinch" procedure previously described by Evans (3, 4). In general, it consists of delivering a graded series of electric shocks through a grid to the feet of the rat. Threshold values are calculated by determining the shock intensities in milliamperes at which the animal "flinches" or "jumps" on 13 of 14 trials. The threshold to "jump" has been found to reflect the action of analgesic drugs.

The modifications of this procedure were: first, only ten series of electric shocks were presented; second, a nine out of ten threshold to jump was calculated rather than the 13 out of 14 threshold; third, an ascending series of shocks was stopped when the animal had "jumped" at three consecutive shock increments and a descending series was terminated by "flinch" responses at three consecutive shock decrements. Finally, since "flinch" thresholds have not previously been found to reflect the analgetic action of drugs, their analysis was not considered in this investigation.

The drugs were administered by intraperitoneal injection one hour prior to testing. The vehicle used to convey the morphine phosphate was composed of 50% ethyl alcohol and 50% isotonic saline solution. No injection exceeded 0.5 cc in volume. Each animal was tested at each of five dose levels of morphine and also on the vehicle alone. A minimum of 48 hours always intervened between tests for a given animal.

The dose levels of morphine phosphate tested were 4 mg/kg, 6 mg/kg, 8 mg/kg, 10 mg/kg, and 12 mg/kg. Thus, each animal was tested six times, five times with morphine phosphate and once with the vehicle alone.

III. RESULTS

Figure 1 presents the dose-response curves for the two groups of animals. The graph shows the dose of morphine as a free base in mg/kg plotted against the threshold in milliamperes of electric shock to "jump" on nine out of ten trials. From this figure, it can be seen that animals from the addiction-prone strain profit more from receiving morphine. This is to say, the amount of electric shock required to elicit the "jump" threshold on nine out of ten trials is elevated for the addiction-prone group when given morphine at the greater doses. Table 1 presents the individual shock thresholds for the rats in milliamperes. Table 2 presents the analyses of variance and trend for the

two groups as well as a comparison between the groups (5). Table 3 presents a Type I analysis of variance of the differences between the mean threshold values for the highest three dose levels of morphine (6). These analyses show that a true difference exists between the addiction-prone and the addiction-resistant groups in terms of both the slope of the dose-response curve for all dose values as well as saline and the mean "jump" thresholds at the higher doses. For the slope index, the probability of the occurrence of this great a difference by chance alone is less than .026 and the analysis of the higher morphine levels shows $p < .05$ for the mean threshold differences.

IV. DISCUSSION

The results of this study indicate that a positive relationship exists between the animals from a strain which is highly liable to addiction and the degree of profit from the actions of morphine as an analgetic agent. At present, it would be premature to attempt a guess as to the basis of this relationship. However, upon the basis of this experiment, certain questions of great interest do arise. First, one might ask, "What are the physiological and psychological differences between the addiction-prone and the addiction-resistant rats which lead both to their differential sensitivity to the analgetic effects of morphine and to its addicting effects?" Second, one would wish to know if we could predict the addiction liability of an animal upon the basis of its response to the analgetic effects of morphine. This would, of course, have to be tested with other strains of rats to determine the generality of the prediction. Finally, and perhaps of the greatest practical importance, would be the question, "Can the addiction liability in a human be predicted upon the basis of a knowledge of that individual's response to the analgetic effects of opiate drugs?" The use of behavioral procedures in the study of opiate addiction and opiate analgesia should be able to lead us further in answering these questions.

V. REFERENCES

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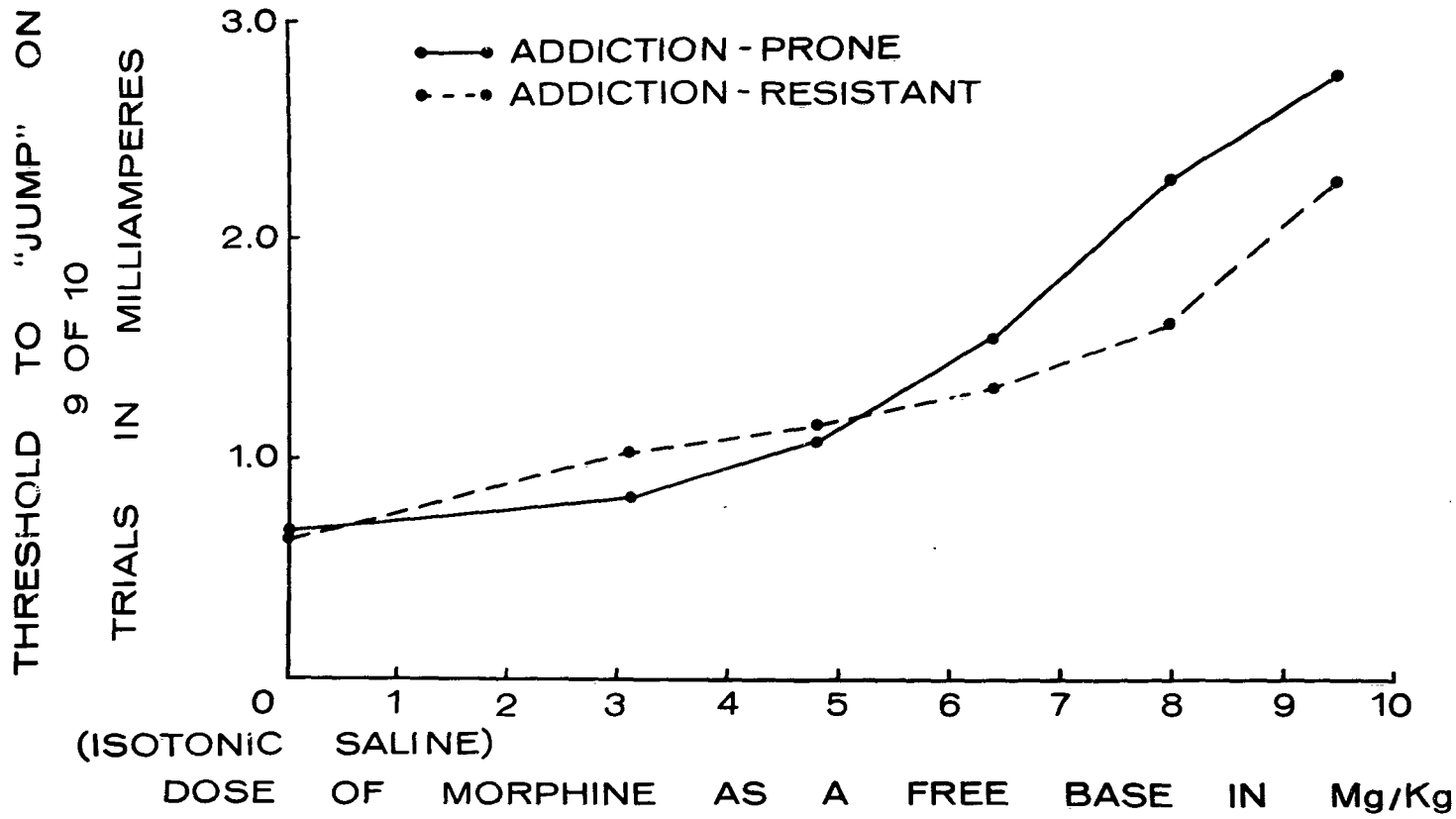
THRESHOLD TO "JUMP" ON 9 OF 10 TRIALS IN MILLIAMPERES
3.0
2.0
1.0
0
ADDICTION - PRONE
ADDICTION - RESISTANT
1
2
3
4
5
6
7
8
9
10
(ISOTONIC SALINE)
DOSE OF MORPHINE AS A FREE BASE IN Mg/Kg

Figure 1

TABLE 1. Scores are jump threshold in milliamperes.

		Morphine Dose Level					
	Rat No.	0	4	6	8	10	12
Addiction-Prone	83	1.01	.93	1.14	1.11	2.73	1.86
	85	.66	.73	1.83	1.17	3.20	3.20
	37	.97	.62	1.11	2.52	1.92	2.73
	33	.56	.66	.61	1.30	2.03	2.82
	39	.63	1.14	1.12	3.20	1.81	3.20
	69	.51	1.03	1.01	.93	1.57	3.20
	71	.62	.76	.82	.91	1.35	1.73
	67	.46	.64	1.01	1.02	3.20	3.20
Mean		.68	.81	1.08	1.52	2.23	2.74
Addiction-Resistant	53	.62	.61	.62	.92	1.74	2.74
	55	.78	1.32	1.01	1.41	1.71	1.43
	77	.48	1.11	1.22	1.35	1.03	1.62
	79	.69	1.60	1.52	1.61	2.13	2.91
	25	.43	.52	.75	1.52	1.68	2.14
	27	.67	.72	1.03	1.02	1.12	3.20
	29	.63	1.40	.81	1.13	1.27	1.22
	31	.51	1.09	2.22	1.51	2.12	2.84
Mean		.60	1.05	1.15	1.31	1.60	2.26

TABLE 2. Analysis of trend.

Source	SS	df	MS	F
	Addiction-Prone			
Individual Deviations from Estimate	77636	28	2773	
Group Deviation from Linearity	35602	4	8401	3.03*
Between Individual Slopes	20674	7	2953	1.06
Between Individual Means	30282	7	4326	1.56
Group Slope	237903	1	237903	85.79***
	Addiction-Resistant			
Individual Deviations from Estimate	40623	28	1451	
Group Deviation from Linearity	12100	4	3025	2.08
Between Individual Slopes	19859	7	2837	1.96
Between Individual Means	27886	7	3984	2.75*
Group Slope	114921	1	114921	79.20***
	Comparison of Groups			
Individual Deviations from Estimate	118258	56	2112	
Group Deviation from Estimate	10200	4	2550	1.21
Between Group Slopes	11064	1	11064	5.24**
Between Group Means	7994	1	7994	3.79*

*$p < .06$

**$p < .026$

***$p < .001$

TABLE 3. Analysis of variance of highest three doses.

Source	SS	df	MS	F
Between S	93854	15	6257	1.239
Between G	23649	1	23649	4.682*
Error B	70710	14	5051	
Within S	199859	32		
D	95033	2	47517	13.123**
G x D	3452	2	1726	< 1
Error W	101374	28	3621	
Total	293713	47		

*$p < .05$

**$p < .001$

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